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TITLE: DEVELOPMENT OF AN ANIMAL MODEL OF THORACOLUMBAR BURST FRACTURE-INDUCED ACUTE SPINAL CORD INJURY

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14. ABSTRACT

Here, we describe the design and development of a controlled spinal cord impactor for use in large animal models of SCI in order to more reliably recreate the human injury. A custom designed spinal cord impactor and mounting platform were fabricated to be placed anteriorly or posteriorly over a large animal (e.g., pig, sheep, dog). Repeated impacts demonstrated predictable results with less than 10% variability at each target force. The average impact duration was 71.2 +/- 6.1 msec. At a 40 Newton target, the output force was 41.5 N +/- 1.7%. With a 25 N target, the output was 23.5 N +/- 2.7%; a 15 N target revealed an output of 15.2 N +/- 9.3%. This novel custom designed spinal cord impactor is capable of reliably delivering precise impacts to the spinal cord and will be utilized in future research to study acute traumatic spinal cord injury in a large animal.

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1. Introduction

Spinal cord injury (SCI) frequently leads to permanent disability following traumatic spine injury. A dramatic increase in blast related spinal burst fracture has been observed in recent armed conflicts (OEF/OIF), with many soldiers suffering debilitating SCI. Rodent research has led to many promising advances in SCI treatment, but successful clinical translation remains elusive. Many factors may contribute to this including inadequate animal models, and many researchers in the SCI community have called for improved large animal models of contusion SCI. Several large animal SCI models have been developed but most use static compression or transaction to create injury, not contusion. There are no models of ventral impact, which causes injury in burst fracture. Weight-drop, produces contusion but is imprecise and unpredictable. Therefore, we set out to develop and validate a large animal model of ventral contusion SCI that is seen in burst fracture using a custom-designed, controlled spinal cord impactor and sustained balloon compression.

2. Keywords

Spinal cord injury, spine trauma, burst fracture, large animal model

3. Accomplishments

Specific Aim 1 – Develop and complete proof of concept for a novel animal model of anterior (ventral) spinal cord injury following simulated vertebral body fracture in which the magnitude of primary injury: impulse load (contusion) + canal compromise (compression) can be controlled and titrated

Building on our previous achievements, we have established that the proposed model is indeed feasible. We have developed a custom automated spinal cord impactor and we have developed techniques and procedures that establish the first large animal model of ventral thoracolumbar spinal cord injury. We have shown that our impactor can generate precise graded impacts to the spinal cord in a live large animal model (Figure 1). We have also demonstrated a predictable and reliable injury response (neurological function) to increasing energy of spinal cord impact (Figure 2). In further animal surgeries we will demonstrate the reliability and fidelity of our model.

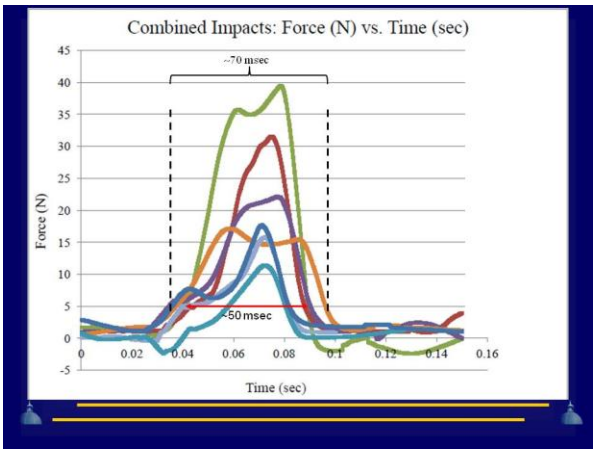

Figure 1. Spinal cord injury impacts. Each line represents a unique injury event in a unique animal.

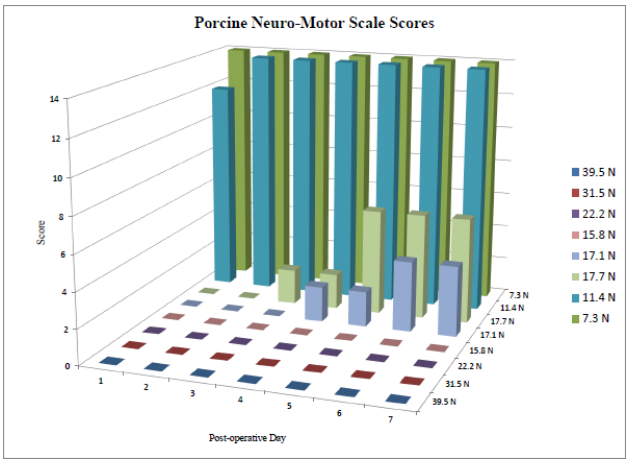

Figure 2. Post-injury neurological function vs. magnitude of injury impact.

Specific Aim 2 – Demonstrate ability to reliably and incrementally adjust contusion impulse load and compression magnitude and duration.

We have shown above (Figure 1) that we have successfully constructed and tested a custom impactor that is capable of delivering reliable and predictable impacts to the spinal cord. We have also shown in preliminary experiments that we can successfully create variable degrees of spinal cord compression in the post contusion injury period. We will continue these experiments to further demonstrate and refine our model of combined contusion and compression.

Specific Aim 3 – Develop and validate a postoperative assessment plan for this animal model.

We have been processing spinal cord tissue from our initial and previous experiments in order to demonstrate the severity of injury in histopathological staining. We have continued to refine our and have sought expertise from within our institution (at no cost) to facilitate processing and analysis of spinal cord tissue. We will continue analysis of the tissue slides in the coming months to further assess the volume of lesions created and the degree of spinal cord injury. We have also developed a post-injury plan of care and assessment that we have utilized to determine neurological function (Figure 2). Furthermore, we have developed methods to analyze imaging results to determine the size of spinal cord injury after impact.

Specific Aim 4 – Utilize this validated model to address future specific aims.

4. Impact

Impact to principal discipline: In these early experiments we have successfully demonstrated the feasibility of a ventral model of thoracolumbar spinal cord injury in a large animal species. This is the first such model of this type of injury. In developing this model, we have designed, built and tested the first fully automated and precision controlled spinal cord impactor. This model and impactor could be used in the future to further define the pathophysiology of spinal cord injury, and is the only model that could be used to investigate ventral thoracolumbar impacts. These types of injuries are often seen in blast events and other traumatic events. We will further define this model and impact device to develop a highly reliable and predictable model of these ventral thoracolumbar injuries.

Impact on other disciplines: The technology of our impactor could be modified with relatively simple changes and be adapted for other purposes. These could include brain injury studies and other models of spinal cord injury. This impactor is the only large animal impactor that reproduces the events of acute contusion type spinal cord injury.

Impact on technology transfer: It is not clear at this point whether any technology developed in our model will be transferred for any other purposes. However, the techniques and procedures we have developed may be used by other investigators to develop other large animal models of spinal cord injury.

Impact on society beyond science and technology: This project will have minimal impact outside of science and technology.

5. Changes/Problems

Changes in approach: As this model is the first of its kind, and this project was designed to demonstrate the feasibility of the model, we have had to make several changes during our study in order to successfully develop the model. These changes have primarily been related to our surgical techniques, custom equipment, and post-operative animal monitoring and care. None of the changes represent a significant departure from our initial proposal, but they are necessary modifications to develop and refine this novel model and custom spinal cord impactor.

Delays and actions to resolve them: The biggest delay in our initial experience involved the analysis and data processing of our pathology slides. Our lab has extensive experience with harvesting and processing spinal cord tissue from many rat models that we have developed. However, the amount of tissue obtained from the pig spinal cords presented a challenge in processing, staining, and analyzing all of the specimens. We especially encountered difficulty when attempting to digitize and analyze the tissue samples. The digital files were so large that they took an unexpectedly large amount of time to process and analyze. Indeed we ultimately had to enlist the expertise of a colleague in our department who helped develop a custom computer program to perform quantitative analysis of the tissue slides for signs of spinal cord injury. Now that we have resolved this major issue, we are continuing with the animal experiments to further refine the contusion compression model.

Expenditures: No changes.

Changes in use of animals: No changes.

6. Products

Publications

Journal publications: We have submitted for publication our manuscript entitled: *Design and development of a controlled spinal cord impactor for use in large animal models of acute traumatic spinal cord injury.* We are awaiting word from the publisher on the acceptance status.

Conference presentations: We presented our initial findings at the 2014 Military Health Services Research Symposium in Fort Lauderdale, Florida.

Technologies and techniques: All of our surgical techniques and our custom impactor are unique products of this project as described above.

7. Participants & Other Collaborating Organizations

Individuals working on the project

PI(s): Daniel M. Sciubba, MD and Brett A. Freedman, MD

Key Personnel

Name: Rory J. Petteys, MD
Role: Lead investigator
Identifier:
Person months worked: 12
Contribution: Dr. Petteys performed all surgical procedures and supervised all post-injury care and procedures for all animals.
Funding Support: This project

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Role: Assistant investigator
Identifier:
Person months worked: 12
Contribution: Dr. Sarabia-Estrada performed much of the animal care and the processing of spinal cord tissue.
Funding Support: Unchanged

Name: Steven M. Spitz, MD

Role: Assistant investigator
Identifier:
Person months worked: 12
Contribution: Dr. Spitz assisted with the surgical procedures and helped supervise the animal care and assessment.
Funding Support:

Change(s) in active/other support of Pis / key personnel: None
Other Organizations Involved: None

8. Special Reporting Requirements - None

9. Appendices - None